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(54) **Antihyperlipidemic and antiatherosclerotic urea and carbamate compounds.**

(57) Certain substituted urea, thiourea, carbamate, and thiocarbamate compounds are potent inhibitors of the enzyme acyl-CoA:cholesterol acyltransferase and are thus useful agents for inhibiting the intestinal absorption of cholesterol, and for lowering blood plasma cholesterol.

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ANTIHYPERLIPIDEMIC AND ANTIATHEROSCLEROTIC UREA AND CARBAMATE COMPOUNDS

This invention relates to chemical compounds having pharmacological activity, to pharmaceutical compositions which include these compounds, and to the use thereof for the preparation of these compositions. More particularly, this invention concerns certain substituted urea and carbamate compounds which inhibit the enzyme acyl-coenzyme A:cholesterol acy-transferase (ACAT), pharmaceutical compositions containing these compounds, and a method of use for the preparation of pharmaceuticals for inhibiting intestinal absorption of cholesterol or of regulating cholesterol.

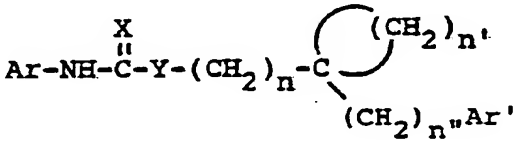
In recent years the role which elevated blood plasma levels of cholesterol plays in pathological conditions in man has received much attention. Deposits of cholesterol in the vascular system have been indicated as causative of a variety of pathological conditions including coronary heart disease.

Initially, studies of this problem were directed toward finding therapeutic agents which would be effective in lowering total serum cholesterol levels. It is now known that cholesterol is transported in the blood in the form of complex particles consisting of a core of cholesterol esters plus triglycerides and an exterior consisting primarily of phospholipids and a variety of types of protein which are recognized by specific receptors. For example, cholesterol is carried to the sites of deposit in blood vessels in the form of low density lipoprotein cholesterol (LDL cholesterol) and away from such sites of deposit by high density lipo-protein cholesterol (HDL cholesterol).

Following these discoveries, the search for therapeutic agents which control serum cholesterol turned to finding compounds which are more selective in their action; that is, agents which are effective in elevating the blood serum levels of HDL cholesterol and/or lowering the levels of LDL cholesterol. While such agents are effective in moderating the levels of serum cholesterol, they have little or no effect on controlling the initial absorption of dietary cholesterol in the body through the intestinal wall.

In intestinal mucosal cells, dietary cholesterol is absorbed as free cholesterol which must be esterified by the action of the enzyme acyl-CoA: cholesterol acyltransferase (ACAT) before it can be packaged into the chylomicrons which are then released into the blood stream. Thus, therapeutic agents which effectively inhibit the action of ACAT prevent the intestinal absorption of dietary cholesterol into the blood stream or the reabsorption of cholesterol which has been previously released into the intestine through the body's own regulatory action.

The present invention provides a class of compounds with ACAT inhibitory activity having the structure



wherein Ar is phenyl or naphthyl. The phenyl or naphthyl group is unsubstituted, or may be optionally substituted with alkyl of from one to six carbon atoms, hydroxy, alkoxy of from one to six carbon atoms, fluorine, chlorine, bromine, nitro, trifluoromethyl, or $-NR_1R_2$ in which R_1 and R_2 are independently hydrogen or alkyl of from one to six carbon atoms.

The atom X is oxygen or sulfur, Y is oxygen or -NH-, n is zero or is an integer of from one to three, n′ is an integer of from two to six, and n″ is zero, one, or two.

Ar′ is selected from phenyl, naphthyl, thienyl, or pyridinyl. Ar′ is unsubstituted, or may be optionally substituted with alkyl of from one to six carbon atoms, hydroxy, alkoxy of from one to six carbon atoms, fluorine, chlorine, bromine, nitro, trifluoromethyl, or $-NR_1R_2$ in which R_1 and R_2 are independently hydrogen or alkyl of from one to six carbon atoms.

The compounds of the present invention form a class of substituted ureas, thioureas, carbamates, and thiocarbamates having potent activity as inhibitors of the enzyme acyl CoA: cholesterol acyltransferase (ACAT). Preferred compounds of the present invention are the urea and thiourea compounds, with the urea compounds being most preferred.

In the urea compounds of the present invention, the first nitrogen atom is monosubstituted by an aromatic ring system selected from phenyl or naphthyl. The phenyl ring is unsubstituted or, alternatively, is substituted with one, two, or three groups selected independently from alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, or $-NR_1R_2$ in which R_1 and R_2 are independently hydrogen or alkyl of from one to six carbon atoms. Preferred

compounds are those in which the aromatic ring system is phenyl or substituted phenyl.

In the urea and thiourea compounds of this invention, the second nitrogen atom is substituted with an aryl-substituted cycloalkyl ring which may be attached directly to the nitrogen atom, or may separated from the nitrogen atom by a bridging group of up to three methylene (i.e.-CH_2-) groups. The cycloalkyl ring is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, with cyclopentyl and cyclohexyl being preferred.

The cycolalkyl ring is further substituted, at the same atom of attachment to the nitrogen of the urea moiety or the same atom of attachment to the methylene bridge, by an aryl group. This aryl group is unsubstituted phenyl, naphthyl, thienyl, or pyridinyl or, alternatively, may be one of these aromatic rings optionally substituted by one, two, or three groups independently selected from alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, or -NR_1R_2 in which R_1 and R_2 are independently hydrogen or alkyl of from one to six carbon atoms. Preferred compounds of this invention are those in which the aromatic ring system attached to the cycloalkyl ring is thienyl or unsubstituted phenyl.

Examples of compounds contemplated as falling within the scope of the invention are the following:

N-(2,6-Dimethylphenyl)-N′-(1-phenylcyclopentyl)urea.
N-(2,6-Diethylphenyl)-N′-(1-phenylcyclobutyl)urea.
N-(2,6-Diethylphenyl)-N′-(1-phenylcyclopentyl)urea.
N-(2,6-Diethylphenyl)-N′-[(1-phenylcyclopropyl)methyl]urea.
N-(1-Phenylcyclopentyl)-N′-(2,4,6-trimethoxyphenyl)urea.
N-(2,6-Dimethylphenyl)-N′-[1-(2-thienyl)cyclohexyl]urea.
N-(2,6-Diethylphenyl)-N′-[1-(2-thienyl)cyclohexyl]urea.
N-[2,6-bis(1-Methylethyl)]-N′-[1-(2-thienyl)cyclohexyl]urea.
N-(2,6-Diethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(2,6-Dimethylphenyl)-N′-[(1-phenylcyclopentyl)methyl]urea.
N-(2,6-Dimethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(2,6-Diethylphenyl)-N′-[(1-phenylcyclopentyl)methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[2-Methyl-6-(1-methylethyl)phenyl]-N′-[1-(2-thienyl)cyclohexyl]urea.
N-[2-(1,1-Dimethylethyl)-6-methylphenyl]-N′-[1-(2-thienyl)cyclohexyl]urea.
N-[2-Methyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[2-(1,1-Dimethylethyl)-6-methylphenyl]-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[2-Ethyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[2-Methyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea.
N-[2-(1,1-Dimethylethyl)-6-methylphenyl]-N′-[(1-phenylcyclopentyl)methyl]urea.
N-[2-Ethyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea.
N-(2,4-Difluorophenyl)-N′-[1-(2-thienyl)-cyclohexyl]urea.
N-(2,4-Difluorophenyl)-N′-[(1-phenylcyclopentyl)methyl]urea.
N-(2,4-Difluorophenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(2,6-Dibromo-4-fluorophenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.

By the term "alkyl" as used throughout this specification and the appended claims is meant a branched or unbranched hydrocarbon grouping derived from a saturated hydrocarbon of from one to six carbon atoms by removal of a single hydrogen atom. Examples of alkyl groups contemplated as falling within the scope of this invention include methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, and 1,1-dimethylethyl.

By the term "alkoxy" is meant an alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom.

In those instances where the compounds of the present invention bear a basic nitrogen atom as, for example, when Ar or Ar′ is substituted by amino, alkylamino, or dialkylamino, or when Ar′ is pyridinyl, the compounds are capable of forming acid addition salts. These acid addition salts are also contemplated as falling within the scope of this invention.

While the acid addition salts may vary from the free base form of the compounds in certain properties such as melting point and solubility, they are considered equivalent to the free base forms for the purposes of this invention.

The acid addition salts may be generated from the free base forms of the compounds by reaction of the latter with one equivalent of a suitable non-toxic, pharmaceutically acceptable acid, followed by evaporation of the solvent employed for the reaction and recrystallization of the salt, if required. The free

base may be recovered from the acid addition salt by reaction of the salt with a water solution of the salt with a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, sodium hydroxide, and the like.

Suitable acids for forming acid addition salts of the compounds of this invention include, but are not necessarily limited to acetic, benzoic, benzenesulfonic, tartaric, hydrobromic, hydrochloric, citric, fumaric, gluconic, glucuronic, glutamic, lactic, malic, maleic, methanesulfonic, pamoic, salicylic, stearic, succinic, sulfuric, and tartaric acids. The class of acids suitable for the formation of non-toxic, pharmaceutically acceptable salts is well known to practitioners of the pharmaceutical formulation arts. (See, for example, Stephen N. Berge, et al. J. Pharm. Sciences, 66:1-19 (1977).

Further, the compounds of this invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

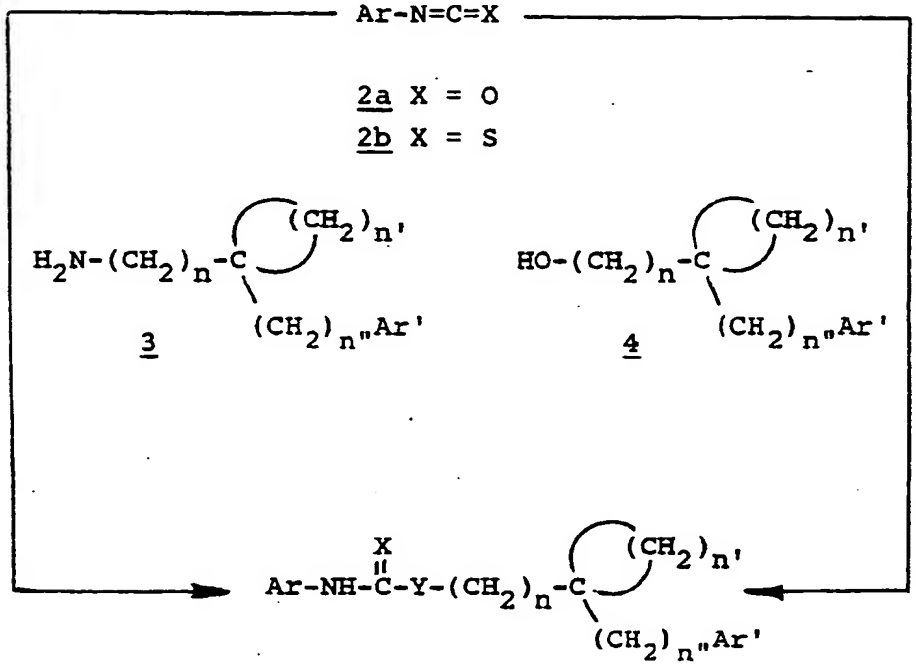
The compounds of the present invention are prepared by the general method outline in Reaction Scheme 1. The appropriately substituted isocyanate, 2a (where X = O), or thioisocyanate compounds, 2b - (where X = S), are reacted with the desired amine, 3, to obtain the substituted urea compounds of the present invention, 1a-1b, or with the desired alcohol, 4, to obtain the substituted carbamate compounds of the present invention, 1c-1d.

The reaction is generally carried out in a polar aprotic organic solvent such as ethyl acetate, at any temperature between room temperature and the boiling point of the solvent, with room temperature being preferred.

The reaction is allowed to proceed until analysis of the mixture by a means such as chromatography indicates that the reaction is substantially complete. Reaction times may vary between about two hours to about 24 hours, depending upon the particular reagents and reaction temperature employed. The starting isocyanate or thioisocyanate compounds are known or commercially available or, if not previously known, are prepared by methods well known in the art from the corresponding amine compounds.

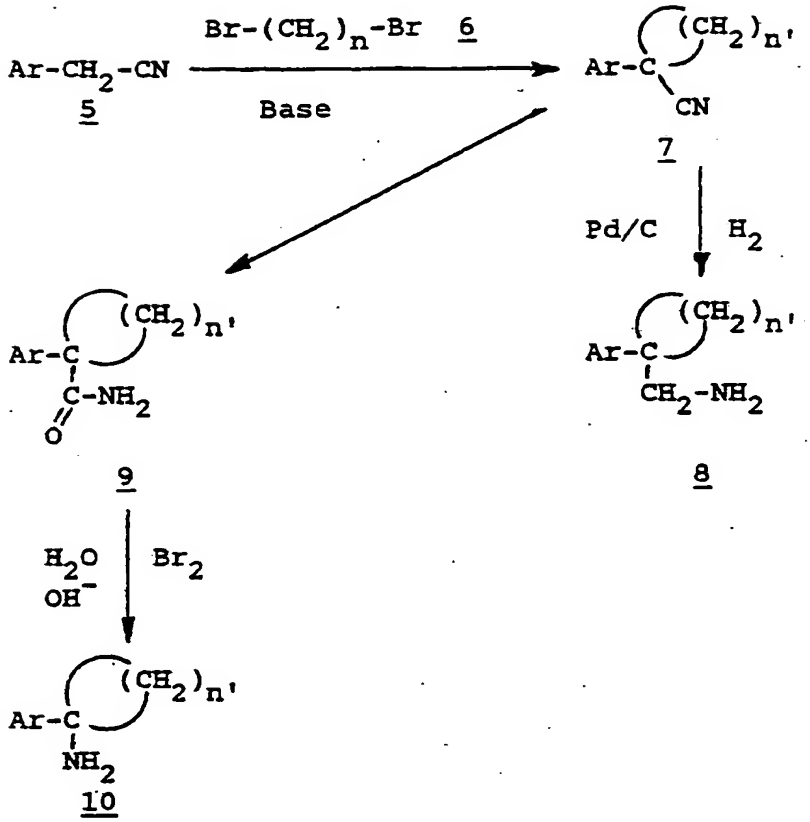
The amine compounds, 3, are prepared by the general method detailed in J. Org. Chem., 36(9): 1308 (1971) and depicted schematically in Reaction Scheme 2. Referring to Reaction Scheme 2, phenylacetonitrile or the substituted phenylacetonitrile 5, is reacted with the desired alpha-omega dibromoalkalne, 6, in the presence of base to produce the cycloalkyl nitrile, 7. This compound

Reaction Scheme 1



1a X = O, Y = NH
1b X = S, Y = NH
1c X = O, Y = O
1d X = S, Y = O

Reaction Scheme 2



is catalytically reduced by the action of hydrogen over a noble metal catalyst to produce the aryl-(aminomethyl)cycloalkane compound, 8. Acid hydrolysis of compound 6, produces the corresponding aryl-(cycloalkyl) carboxamide, 9, which is then subjected to the Hofmann degradation reaction (Ber., 14: 2725 (1881)) to produce the aryl(cycloalkyl)amine 10.

As shown by the data presented below in Table 1, the compounds of the present invention are potent inhibitors of the enzyme acyl-CoA:cholesterol acyltransferase (ACAT), and are thus effective in inhibiting the esterification and transport of cholesterol across the intestinal cell wall. The compounds of the present invention are thus useful in pharmaceutical formulations for the inhibition of intestinal absorption of dietary cholesterol, the reabsorption of cholesterol released into the intestine by normal body action, or the modulation of cholesterol.

In Vitro Tests

The ability of representative compounds of the present invention to inhibit ACAT was measured using an in vitro test more fully described in Field, F. J. and Salone, R. G., Biochemica et Biophysica 712: 557-570 (1982). The test assesses the ability of a test compound to inhibit the acylation of cholesterol by oleic

acid by measuring the amount of radio-labeled cholesterol oleate formed from radio-labeled oleic acid in a tissue preparation containing rabbit intestinal microsomes.

The data appear in Table 1 where they are expressed as IC_{50} values; i.e. the concentration of test compound required to inhibit 50% expression of the enzyme.

Table 1

Compound of Example	IC_{50} (Micromolar)
1	0.08
2	0.23
3	0.12
4	0.088
5	0.70
6	0.13
7	0.048
8	0.043
9	0.051
10	0.154
11	0.081
12	0.015
13	0.017
14	0.021
15	0.23
16	0.256
17	0.058
18	0.054
19	0.020
20	0.016
21	0.018
22	0.025
23	0.37
24	1.28
25	0.79
26	0.039

In Vivo Tests

In one in vivo screen, designated PCC, male Sprague-Dawley rats (approximately 200 g body weight) are randomly divided into groups and provided ad libidum a regular chow diet (Purina No. 5002, Ralston Purina Co., 711 West Fuesser Road, Mascoutah, Illinois, 62224, USA), supplemented with 5.5% peanut oil, 1.5% cholesterol, and 0.3%-0.5% cholic acid, together with 0.05% of the test drug which is admixed into the diet. After one week the animals are etherized and a blood sample is taken from the heart and mixed with 0.14% ethylenediamine tetraacetic acid (EDTA) to measure the total cholesterol. The results of this trial for representative compounds of the present invention appear in Table 2.

Table 2

Compound of Example	Total Blood Cholesterol (mg/dl)	% Change
13	61 (Control = 224)	-73
8	60 (Control = 181)	-69

In therapeutic use as agents for the inhibition of intestinal absorption of cholesterol, or as hypolipidemic or hypocholesterolemic agents, the compounds utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from 250 to 1000 mg per day. For a normal human adult of approximately 70 kg of body weight, this translates into a dosage of from 5 to 20 mg/kg of body weight per day. The specific dosages employed, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, and cachets.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Powders and tablets preferably contain between about 5 to about 70% by weight of the active ingredient. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions suitable for oral administration, or suspensions and emulsions suitable for oral administration. Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

The following preparative examples are provided to enable one skilled in the art to practice the invention, and are illustrative thereof. They are not to be read as limiting the scope of the invention as it is

defined by the appended claims.

Example 1

Preparation of N-(2,6-dimethylphenyl)-N′-(1-phenylcyclopentyl)urea

To a solution of 1-phenylcyclopentyl amine (1.0 g, 0.006 mole) in 30 ml of ethylacetate, 2,6-dimethylphenyl isocyanate (0.91 g, 0.006 mole) is added and the reaction mixture is stirred at room temperature for 20 hours Volatiles are removed under reduced pressure and the residue is crystallized from ethylacetate-hexane yielding 1.65 g of N-(2,6-dimethylphenyl -N′-(1-phenylcyclopentyl)urea having a melting point of 227-229 °C

Analysis calculated for $C_{20}H_{24}N_2O$

C = 77.88, H = 7.84; N = 9.08

Found

C = 77.72; H = 7.83; N = 9.19

Example 2

Preparation of N-(2,6-diethylphenyl)-N′-(1-phenylcyclobutyl)urea

To a solution of 1-phenylcyclobutyl amine (1.0g, 0.0057 mole) in 30 ml of ethylacetate, 2,6-diethylphenylisocyanate (0.84 g, 0.0057 mole) is added and the reaction mixture is stirred at room temperature for 20 hours. Precipitated solid is filtered, washed with ethylacetate and dried yielding 1.46 g of N-(2, 6-diethylphenyl)-N′-(1-phenylcyclobutyl)urea having a melting point of 227-230 °C.

Analysis calculated for $C_{21}H_{26}N_{20}$

C = 78.22; H = 8.12; N = 8.68

Found

C = 78.43; H = 8.32; N = 8.89

Example 3

Preparation of N-(2,6-diethylphenyl)-N′-(1-phenylcyclopentyl)urea

The title compound is prepared according to the procedure described for the Example 2. Melting point 215-218 °C.

Analysis calculated for $C_{22}H_{28}N_2O$

C = 78.53; H = 8.38; N = 8.32

Found

C = 78.35, H = 8.34; N = 8.19

Example 4

Preparation of N-(2,6-diethylphenyl)-N′-[(1-phenylcyclopropyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 166-168° C
Analysis calculated for $C_{21}H_{26}N_2O$
C = 78.22; H = 8.12; N = 8.68
Found
C = 78.13; H = 8.28; N = 8.63

Example 5

Preparation of N-(1-phenylcyclopentyl)-N′-(2,4,6-trimethoxyphenyl)urea

The title compound is prepared according to Example 2. Melting point 193-195° C
Analysis calculated for $C_{21}H_{26}N_2O_4$
C = 68.09; H = 7.07; N = 7.56
Found
C = 67.75; H = 6.85; N = 7.34

Example 6

Preparation of N-(2,6-dimethylphenyl)-N′-[1-(2-thienyl)cyclohexyl]urea

The title compound is prepared according to Example 2. Melting point 220-222° C.
Analysis calculated for $C_{19}H_{24}N_2OS$
C = 69.47; H = 7.36; N = 8.52, S = 9.76
Found
C = 69.43; H = 7.24; N = 8.69; S = 9.87

Example 7

Preparation of N-(2,6-diethylphenyl)-N′-[1-(2-thienyl)cyclohexyl]urea

The title compound is prepared according to Example 2. Melting Point 208-210° C
Analysis calculated for $C_{21}H_{28}N_2OS$
C = 70.75; H = 7.91; N = 7.85; S = 8.99
Found
C = 71.02; H = 8.08; N = 7.93; S = 9.08

Example 8

Preparation of N-[2,6-bis(1-methylethyl)]-N′-[1-(2-thienyl)cyclohexyl]urea

The title compound is prepared according to Example 2. Melting point 170-171 °C.
Analysis calculated for $C_{23}H_{32}N_2OS$
C = 71.83; H = 8.38; N = 7.28; S = 8.33
Found
C = 72.18; H = 8.48; N = 7.37, S = 8.64

Example 9

Preparation of N-(2,6-diethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 185-186 °C.
Analysis calculated for $C_{24}H_{32}N_2O$
C = 79.08; H = 8.84; N = 7.68
Found
C = 79.42; H = 8.95; N = 7.70

Example 10

Preparation of N-(2,6-dimethylphenyl)-N′-[(1-phenylcyclopentyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 201-202 °C.
Analysis calculated for $C_{21}H_{26}N_2O$
C = 78.22; H = 8.12; N = 8.68
Found
C = 77.92; H = 8.05; N = 8.64

Example 11

Preparation of N-(2,6-dimethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 207-208 °C.
Analysis calculated for $C_{22}H_{28}N_2O$
C = 78.53; H = 8.38; N = 8.32
Found
C = 78.59; H = 8.37; N = 8.46

Example 12

Preparation of N-(2,6-diethylphenyl)-N′-[(1-phenylcyclopentyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 165-167° C.
Analysis calculated for $C_{23}H_{30}N_2O$
C = 78.62; H = 8.62; N = 7.99
Found
C = 78.54; H = 8.48; N = 7.93

Example 13

Preparation of N-[2,6-bis(1-methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 181-183° C.
Analysis calculated for $C_{25}H_{34}N_2O$
C = 79.32; H = 9.05; N = 7.39
Found
C = 79.01; H = 8.97; N = 7.21

Example 14

Preparation of N-[2,6-bis(1-methylethyl)phenyl-N′-[(1-phenylcyclohexyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 168-169° C.
Analysis calculated for $C_{26}H_{36}N_2O$
C = 79.55; H = 9.24; N = 7.13
Found
C = 79.31; H = 8.99; N = 7.06

Example 15

Preparation of N-[2-methyl-6-(1-methylethyl)-phenyl]-N′-[1-(2-thienyl)cyclohexyl]urea

The title compound is prepared according to Example 2. Melting point 230-232° C.
Analysis calculated for $C_{21}H_{28}N_2OS$
C = 70.74; H = 7.91; N = 7.85; S = 8.99
Found
C = 70.53; H = 7.88; N = 8.03; S = 8.90

Example 16

Preparation of N-[2-(1,1-dimethylethyl)-6-methyl-phenyl]-N′-[1-(2-thienyl)cyclohexyl]urea

The title compound is prepared according to Example 2. Melting point 245-246° C.
Analysis calculated for $C_{22}H_{30}N_2OS$
C = 71.31; H = 8.16; N = 7.55; S = 8.65
Found
C = 71.51; H = 8.19; N = 7.53; S = 8.43

Example 17

Preparation of N-[2-methyl-6-(1-methylethyl)-phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 158-160° C.
Analysis calculated for $C_{24}H_{32}N_2O$
C = 79.08; H = 8.84; N = 7.68
Found
C = 78.75; H = 8.89; N = 7.76

Example 18

Preparation of N-[2-(1,1-dimethylethyl)-6-methylphenyl]-N′-[(1-phenylcyclohexyl)methyl]-urea

The title compound is prepared according to Example 2. Melting point 196-197° C.
Analysis calculated for $C_{25}H_{34}N_2O$
C = 79.32; H = 9.05; N = 7.39
Found
C = 79.11; H = 9.27; N = 7.36

Example 19

Preparation of N-[2-ethyl-6-(1-methylethyl)-phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 178-180° C.
Analysis calculated for $C_{25}H_{34}N_2O$
C = 79.32; H = 9.05; N = 7.39
Found
C = 79.62; H = 9.17; N = 7.47

Example 20

Preparation of N-[2-methyl-6-(1-methylethyl)-phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 157-159° C.
Analysis calculated for $C_{23}H_{30}N_2O$
C = 78.81; H = 8.62; N = 7.99
Found
C = 78.48; H = 8.61; N = 7.93

Example 21

Preparation of N-[2-(1,1-dimethylethyl)-6-methylphenyl]-N′-[(1-phenylcyclopentyl)methyl]-urea

The title compound is prepared according to Example 2. Melting point 196-197° C.
Analysis calculated for $C_{24}H_{32}N_2O$
C = 79.08; H = 8.84; N = 7.68
Found
C = 78.65; H = 9.01; N = 7.58

Example 22

Preparation of N-[2-ethyl-6-(1-methylethyl)-phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 152-154° C.
Analysis calculated for $C_{24}H_{32}N_2O$
C = 79.08; H = 8.84; N = 7.68
Found
C = 79.17; H = 9.05; N = 7.65

Example 23

Preparation of N-(2,4-difluorophenyl)-N′-[1-(2-thienyl)cyclohexyl]urea

The title compound is prepared according to Example 1. Melting point 175-177° C.
Analysis calculated for $C_{17}H_{18}N_2OSF_2$
C = 60.70; H = 5.39; N = 8.32; S = 9.53
Found
C = 60.80; H = 5.50; N = 8.31; S = 9.62

Example 24

Preparation of N-(2,4-difluorophenyl)-N′-[(1-phenylcyclopentyl)methyl]urea

The title compound is prepared according to Example 1. Melting point 160-161° C.
Analysis calculated for $C_{19}H_{20}N_2OF_2$
C = 69.08; H = 6.10; N = 8.47; F = 11.49
Found
C = 68.94; H = 6.09; N = 8.32; F = 11.55

Example 25

Preparation of N-(2,4-difluorophenyl)-N′-[(1-phenylcyclohexyl)methyl]urea

The title compound is prepared according to Example 1. Melting point 163-165° C.
Analysis calculated for $C_{20}H_{22}N_2OF_2$
C = 69.75; H = 6.43; N = 8.13; F = 11.03
Found
C = 69.58; H = 6.56; N = 8.04; F = 10.87

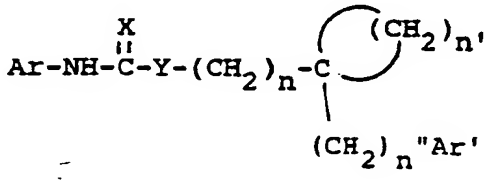
Example 26

Preparation of N-(2,6-dibromo-4-fluorophenyl)-N′-[(1-phenyl-cyclohexyl)methyl]urea

The title compound is prepared according to Example 2. Melting point 196-198° C.
Analysis calculated for $C_{20}H_{21}N_2OBr_2F$
C = 49.61; H = 4.37; N = 5.78; Br = 33.0; F = 3.92
Found
C = 49.66; H = 4.32; N = 5.68; Br = 32.72; F = 3.80

Claims

1. A compound having the formula



wherein Ar is unsubstituted
phenyl or
naphthyl, or
phenyl or naphthyl substituted with

alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms,
hydroxy,
fluorine,

chlorine,
bromine,
nitro,
trifluoromethyl, or
$-NR_1R_2$ wherein

R_1 and R_2 are independently
hydrogen, or
alkyl of from one to six carbon atoms;

X is oxygen or sulfur;
Y is oxygen or -NH-;
n is zero or is an integer of from one to three;
n' is an integer of from two to six; and
n'' is zero, one, or two;
Ar' is selected from the group
phenyl,
naphthyl,
thienyl or
pyridinyl, which may be unsubstituted or substituted with

alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl, or
$-NR_1R_2$ wherein

R_1 and R_2 are independently
hydrogen or
alkyl of from one to six carbon atoms;

or a pharmaceutically acceptable salt thereof.

2. A compound as defined by Claim 1 wherein X is oxygen.

3. A compound as defined by Claim 1 wherein Y is -NH-.

4. A compound as defined by Claim 1 wherein Ar is phenyl or phenyl optionally substituted by
alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl, or
$-NR_1R_2$ wherein

R_1 and R_2 are independently hydrogen, or
alkyl of from one to six carbon atoms.

5. A compound as defined by Claim 1 wherein Ar' is selected from unsubstituted
thienyl or
phenyl; or
phenyl or thienyl substituted with

alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl, or
$-NR_1R_2$ wherein

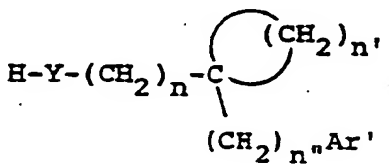
R_1 and R_2 are independently
hydrogen or
alkyl of from one to six carbon atoms.

6. A compound as defined by Claim 1 selected from the group N-(2,6-dimethylphenyl)-N′-(phenylcyclopentyl)urea;
N-(2,6-diethylphenyl)-N′-(1-phenylcyclobutyl)urea;
N-(2,6-diethylphenyl)-N′-(1-phenylcyclopentyl)urea;
N-(2,6-diethylphenyl)-N′- [(-phenylcyclopropyl)methyl]urea;
N-(1-phenylcyclopentyl)-N′-(2,4,6-trimethoxyphenyl)urea;
N-(2,6-dimethylphenyl)-N′-[1-(2-thienyl)cyclohexyl]urea;
N-(2,6-diethylphenyl)-N′-[1-(2-thienyl)cyclohexyl]urea;
N-[2,6-bis(1-methylethyl]-N′-[1-(2-thienyl)cyclohexyl]urea;
N-(2,6-diethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea;
N-(2,6-dimethylphenyl)-N′-[(1-phenylcyclopentyl)methyl]urea;
N-(2,6-dimethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea;
N-(2,6-diethylphenyl)-N′-[(1-phenylcyclopentyl)methyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N′ [(1-phenylcyclopentyl)methyl]urea,
N-[2,6-bis(1-methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl[urea;
N-[2-methyl-6-(1-methylethyl)phenyl]-N′-[1-(2-thienyl)cyclohexyl]urea;
N-[2-(1,1-dimethylethyl)-6-methylphenyl]-N′-[1-(2-thienyl)cyclohexyl]urea;
N-[2-methyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea;
N-[2-(1,1-dimethylethyl)-6-methylphenyl]-N′-[(1-phenylcyclohexyl)methyl]urea;
N-[2-ethyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea;
N-[2-methyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea;
N-[2-(1,1-dimethylethyl)-6-methylphenyl]-N′-[(1-phenylcyclopentyl)methyl]urea;
N-[2-ethyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea;
N-(2,4-difluorophenyl)-N′-[1-(2-thienyl)cyclohexyl]urea;
N-(2,4-difluorophenyl)-N′-[(1-phenylcyclopentyl)methyl]urea;
N-(2,4-difluorophenyl)-N′-[(1-phenylcyclohexyl)methyl]urea; or
N-(2,6-dibromo-4-fluorophenyl)-N′- [(1-phenylcyclohexyl)methyl]urea.

7. A pharmaceutical composition for regulating cholesterol comprising an ACAT-inhibitory effective amount of a compound as defined by Claim 1 in combination with a pharmaceutically acceptable carrier.

8. A method of use of a compound according to claims 1 to 6 for the preparation of pharmaceuticals for the inhibition of intestinal absorption of cholesterol or for regulation cholesterol.

9. A method of preparing a compound according to claims 1 to 6 comprising the steps of
a) reacting a compound of the formula
Ar-N=C=O
wherein Ar is as defined above with a compound having the formula



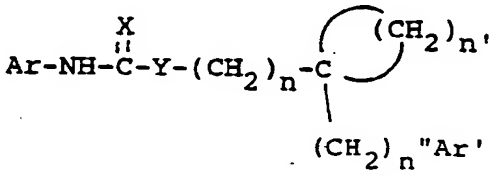
wherein Y, n, n′, n″, and Ar′ are as defined above in a polar aprotic organic solvent at ambient temperature;

b) thereafter isolating the product of said reaction step; and

c) if desired, converting said isolated product to a pharmaceutically acceptable salt.

Claims for the following Contracting States: ES, GR:

1. A process for the preparation of a compound having the formula



wherein Ar is unsubstituted
phenyl or
naphthyl, or
phenyl or naphthyl substituted with

alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl, or
$-NR_1R_2$ wherein

R_1 and R_2 are independently
hydrogen, or
alkyl of from one to six carbon atoms;

X is oxygen or sulfur;
Y is oxygen or -NH-;
n is zero or is an integer of from one to three;
n′ is an integer of from two to six; and
n″ is zero, one, or two;
Ar′ is selected from the group
phenyl,
naphthyl,
thienyl or
pyridinyl, which may be unsubstituted or substituted with

alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl, or
$-NR_1R_2$ wherein

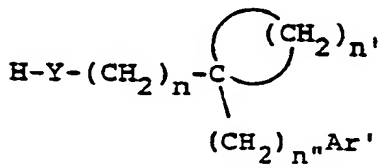
R_1 and R_2 are independently
hydrogen or
alkyl of from one to six carbon atoms;

or a pharmaceutically acceptable salt thereof, comprising the steps of

a) reacting a compound of the formula

Ar-N=C=O

wherein Ar is as defined above with a compound having the formula



wherein Y, n, n′, n″, and Ar′ are as defined above in a polar aprotic organic solvent at ambient temperature;

b) thereafter isolating the product of said reaction step; and

c) if desired, converting said isolated product to a pharmaceutically acceptable salt.

2. A process for the preparation of a compound as defined by Claim 1 wherein X is oxygen.

3. A process for the preparation of a compound as defined by Claim 1 wherein Y is -NH-.

4. A process for the preparation of a compound as defined by Claim 1 wherein Ar is phenyl or phenyl optionally substituted by
alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl, or
$-NR_1R_2$ wherein

R_1 and R_2 are independently
hydrogen, or
alkyl of from one to six carbon atoms.

5. A process for the preparation of a compound as defined by Claim 1 wherein Ar is selected from
unsubstituted
thienyl or
phenyl; or
phenyl or thienyl substituted with

alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl, or
$-NR_1R_2$ wherein

R_1 and R_2 are independently
hydrogen or
alkyl of from one to six carbon atoms.

6. A process for the preparation of a compound as defined by Claim 1 selected from the group
N-(2,6-diethylphenyl)-N′-(phenylcyclopentyl)urea;
N-(2,6-diethylphenyl)-N′-(1-phenylcyclobutyl)urea;
N-(2,6-diethylphenyl)-N′-(1-phenylcyclopentyl)urea;
N-(2,6-diethylphenyl)-N′- [(-phenylcyclopropyl)methyl]urea;
N-(1-phenylcyclopentyl)-N′-(2,4,6-trimethoxyphenyl)urea;
N-(2,6-dimethylphenyl)-N′-[1-(2-thienyl)cyclohexyl]urea;
N-(2,6-diethylphenyl)-N′-[1-(2-thienyl)cyclohexyl]urea;
N-[2,6-bis(1-methylethyl]-N′-[1-(2-thienyl)cyclohexyl]urea;
N-(2,6-diethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea;
N-(2,6-dimethylphenyl)-N′-[(1-phenylcyclopentyl)methyl]urea;
N-(2,6-dimethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea;
N-(2,6-diethylphenyl)-N′-[(1-phenylcyclopentyl)methyl]urea;
N-[2,6-bis(1-methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea,
N-[2,6-bis(1-methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea;
N-[2-methyl-6-(1-methylethyl)phenyl]-N′-[1-(2-thienyl)cyclohexyl]urea;
N-[2-(1,1-dimethylethyl)-6-methylphenyl]-N′-[1-(2-thienyl)cyclohexyl]urea;
N-[2-methyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea;
N-[2-(1,1-dimethylethyl)-6-methylphenyl]-N′-[(1-phenylcyclohexyl)methyl]urea;
N-[2-ethyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea;
N-[2-methyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea;
N-[2-(1,1-dimethylethyl)-6-methylphenyl]-N′-[(1-phenylcyclopentyl)methyl]urea;
N-[2-ethyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea;
N-(2,4-difluorophenyl)-N′-[1-(2-thienyl)cyclohexyl]urea;
N-(2,4-difluorophenyl)-N′-[(1-phenylcyclopentyl)methyl]urea;
N-(2,4-difluorophenyl)-N′-[(1-phenylcyclohexyl)methyl]urea; or
N-(2,6-dibromo-4-fluorophenyl)-N′- [[(1-phenylcyclohexyl)methyl]urea.

7. A method of use of a compound according to claims 1 to 6 for the preparation of pharmaceuticals for the inhibition of intestinal absorption of cholesterol or for regulation cholesterol.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 10 8816

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	DD-A- 154 216 (CHEMISCHE WERKE HUELS AG) * table 1; pages 17-19, claim 1 *	1	C 07 C 127/19 C 07 C 125/065 C 07 C 155/03 C 07 C 157/09 C 07 D 333/14 A 61 K 31/17 A 61 K 31/325
A	EP-A-0 049 538 (BAYER AG) * claim 1 *	1,7	
A	US-A-4 623 662 (V.G. DE VRIES) * claim 1 *	1,7	
A	US-A-4 387 105 (V.G. DE VRIES) * claim 1 *	1,7	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 C 127/19
C 07 C 125/065
C 07 C 155/03
C 07 C 157/09
C 07 D 333/14
A 61 K 31/17
A 61 K 31/325

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	23-08-1988	KAPTEYN H G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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